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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FALK, ANNE MARIE	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/667,998	DOLLY ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *7-9 and 12-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,10,11 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/18/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed October 23, 2006 has been entered. Claims 1-3 and 13-24 have been amended. Claim 25 has been newly added.

Applicants' election without traverse of Group I, Claims 1-11 and 25, is acknowledged. The elected invention is directed to a method for extending the effective time period during which tissue treated with a clostridial toxin is paralyzed comprising administering a composition comprising an agent able to prevent the neuroregenerative activity of a polypeptide as recited in the claims (various neurotrophic factors). Applicants further elected the species IGF-1, from among the various polypeptides, and the species of a binding protein other than an antibody, from among the various agents.

The restriction requirement is still deemed proper and is therefore made FINAL.

Claims 7-9 and 12-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on October 23, 2006.

Claims 1-6, 10, 11, and 25 are examined herein. The claims are examined herein only to the extent that they encompass the elected subject matter and further to the extent necessary to determine patentability of the generic claims.

Claim Objections

Claims 1-6, 10, 11, and 25 are objected to for encompassing non-elected subject matter. In view of the rejection of the generic claims, non-elected species should be deleted from the claims. Following an election of species requirement, when no generic claim is finally held to be allowable, the claims are restricted to the elected species. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 1-6, 10, 11 and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the rejection set forth below, CNTF has been selected as exemplifying the written description issues pertaining to the various neurotrophic factors recited in the claims, thus demonstrating that the generic claim is not allowable. The arguments presented below, however, apply to the broad scope of the claim covering all recited neurotrophic factors other than IGF-1. As for IGF-1, adequate written description is found for the use of IGFBP4 in binding to and blocking the activity of IGF-1 sufficient to extend the period of paralysis of the treated tissue. While the arguments set forth below are not limited to CNTF, for clarity the discussion is directed to CNTF as an example.

The claims encompass and are directed to a method for extending the effective time tissue is paralyzed with a clostridial toxin comprising administering an agent that prevents the expression of a ciliary neurotrophic factor (CNTF) gene. However, the specification does not disclose any agent that can be used in the claimed method. In the absence of a written description of the inhibitory agent, the claimed method lacks written description because the inhibitory agent is an essential element of the claimed method. The specification does not disclose the nucleotide sequence of any ribozyme or antisense molecule that can be used to inhibit the expression of a CNTF gene, nor does the specification disclose any other agent that can be used to inhibit the expression of a CNTF gene. In Example 3, the

specification discusses the use of a ribozyme directed to neural agrin mRNA, but the nucleotide sequence of this ribozyme is not disclosed. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In this case, no CNTF gene inhibitor is disclosed. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In this case, only general teachings are provided for the development of antisense and ribozyme molecules. While the skilled artisan may develop a variety of molecules using these general guidelines, there is insufficient guidance regarding which molecules will function *in vivo* in the manner intended. This limited information regarding the contemplated embodiments is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the full scope of agents for the inhibition of CNTF gene expression or inhibition of expression of any other polypeptide recited in the claims. Thus, it is concluded that the written description requirement is not satisfied for methods of using the genus of agents recited in the claims.

Enablement

Claims 1-6, 10, 11 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of IGF-BP4 to bind and inhibit the activity of IGF-1 in the claimed method for extending the effective period during which tissue treated with a clostridial toxin is paralyzed, wherein said tissue is contacted with a composition comprising IGF-BP4 and a clostridial neurotoxin effective to extend the period of paralysis as compared to treatment with clostridial toxin alone, does not reasonably provide enablement for the full scope of the claims, wherein any one of the polypeptides recited in Claim 25 is inhibited by an agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In the rejection set forth below, CNTF has been selected as exemplifying the enablement issues pertaining to the various neurotrophic factors recited in the claims, thus demonstrating that the generic claim is not allowable. The arguments presented below, however, apply to the broad scope of the claim covering all recited neurotrophic factors other than IGF-1. As for IGF-1, adequate enablement is found for the use of IGFBP4 in binding to and blocking the activity of IGF-1 sufficient to extend the period of paralysis of the treated tissue. While the arguments set forth below are not limited to CNTF, for clarity the discussion is directed to CNTF as an example.

The claims are directed to a method for extending the effective time tissue is paralyzed with a clostridial toxin comprising administering an agent that prevents the expression of a ciliary neurotrophic factor (CNTF) gene. While the claims encompass the use of any agent to inhibit the expression of CNTF genes, the specification only explicitly contemplates the use of antisense and ribozymes. The specification does not provide any teachings for the use of agents other than antisense or ribozymes. Thus, the enablement rejection advanced herein below is directed specifically to the use of antisense and ribozymes, but applies broadly to the use of any agent that will inhibit the expression of a CNTF gene.

The specification fails to provide an enabling disclosure for the method comprising inhibiting the expression of CNTF genes because the *in vivo* function of antisense and ribozymes is unpredictable. Furthermore, as discussed above only general teachings are provided for the design of ribozyme and antisense molecules. No specific molecules are disclosed. Moreover, the specification does not teach how to use a ribozyme molecule that specifically cleaves CNTF mRNA or an antisense molecule that specifically inhibits CNTF expression. The specification only teaches a single mode of delivery wherein the antisense or ribozyme molecule is conjugated to the clostridial toxin. However, the claims specifically recite administering the ribozyme or antisense nucleic acid prior to the administration of clostridial toxin, but the specification does not teach how to deliver the antisense or ribozyme nucleic acid when not linked to the toxin. The specification discusses neural agrin mRNA-specific ribozymes (though

it does not teach their nucleotide sequence), but does not teach ribozymes specific for CNTF mRNA. Dietz (US Patent No. 5,814,500) teaches that many studies with antisense show that gene expression is suppressed by 80-90% of the normal level, but that such reduction is not typically sufficient to reduce the biological effect, i.e., 10-20% expression is sufficient to maintain the biological function sought to be suppressed. The same is true for ribozymes. Baier et al. (1994) also reveal that significant reduction in target mRNA levels as a consequence of ribozyme activity is often not accompanied by reduced expression of the corresponding target protein (last sentence of Abstract and p. 930, column 1, paragraphs 2 and 3). Thus, it is not a routine matter to design antisense and ribozyme molecules appropriate to induce the degree of inhibition necessary to produce the desired effect. Varying degrees of *in vivo* stability of the hybrid leads to varying degrees of inhibition. Accordingly, the *in vivo* effect of any particular ribozyme construct or antisense molecule cannot be predicted. Thus, the success of the method for inhibiting CNTF gene expression *in vivo* relies on the specific design of the antisense or ribozyme construct. In the absence of specific guidance, one skilled in the art would not know how to design ribozymes or antisense targeted to any gene, including those targeted to CNTF mRNA, to achieve a desired level of expression inhibition to produce a desired effect. Furthermore, the operability of the claimed method *in vivo*, in any animal, depends on a number of factors. Good et al. (1997) disclose that the effective intracellular expression of small RNA therapeutics, whether antisense, ribozyme, or RNA aptamer, requires that the RNA be efficiently transcribed, stabilized against rapid degradation, folded correctly, and directed to the part of the cell where it can be most effective (Abstract). The specification does not provide specific guidance for inhibiting CNTF gene expression or inhibiting of expression of any other polypeptide recited in the claims. Thus, the specification does not teach how to produce the desired effect *in vivo* using ribozyme and antisense constructs. In the absence of specific guidance, for producing the desired effect as a consequence of the introduction of a ribozyme or antisense construct, one skilled in the art would not know how to use the claimed method. Furthermore, in the absence of specific guidance

regarding the design of a ribozyme or antisense molecule to produce a desired effect, one skilled in the art would not know how to make the compositions necessary for use in the claimed method.

Given that specific effects cannot be predictably achieved by merely transferring a ribozyme or antisense nucleic acid into a tissue, specific guidance must be provided in the disclosure to enable the instant invention. The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. The claims encompass a method for controlling the expression of a CNTF gene in any animal, but the specification does not enable such a method. Given the limited working examples, the broad scope of the claims, the limited guidance in the specification, and the unpredictability of ribozyme and antisense design for *in vivo* applications, undue experimentation would have been required to practice the claimed method to achieve the claimed effect.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 10, 11, and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6, 10, 11, and 25 are indefinite in their recitation of the conclusory phrase "wherein neural sprouting in said treated tissue is inhibited" (see Claim 1, last line). The preamble recites "a method for extending the effective period during which tissue treated with a clostridial toxin is paralyzed." Thus, the outcome is in conflict with the stated goal of the preamble. Appropriate correction is required.

Claims 1-6, 10, 11, and 25 are indefinite in their recitation of "an agent able to prevent the expression of a neurotrophic polypeptide" and dependent claims that recite agents that do not function by preventing **expression** of the neurotrophic polypeptide, but instead bind to the polypeptide after it is

expressed and inhibit its activity. For example, a binding protein such as IGF-BP4 does not prevent **expression** of IGF-1, but instead binds to IGF-1 and inhibits its activity.

Claim 11 is indefinite in its recitation of "said binding protein" because the phrase lacks antecedent basis in Claim 9. Claim 9 is limited to the use of an agent that prevents expression of a gene encoding said polypeptide. It appears that Claim 11 should depend from Claim 10, which recites that the agent is a binding protein other than an antibody. Appropriate correction is required.

Conclusion

No claim is allowable.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER